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Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumour, trauma or failed arthroplasty

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ABSTRACT

Introduction: Infection in megaprostheses remains an unsolved problem, with a rate of occurrence ranging from 5% to 12%. Silver coating of medical devices has recently been proposed to reduce infection rate because of the antibacterial effect of silver. This innovation could be particularly interesting for megaprostheses, but few data have been reported in the literature.

Materials and methods: From June 2010 to August 2014 a modified MegaC System megaprosthesis with an innovative peripheral silver-added layer of titanium alloy ('Porag') was implanted in 33 patients after previous infection (21 patients) or at high risk for infection because of local or general conditions (12 patients). Previous infection followed megaprosthesis or standard arthroplasty procedures in 14 patients and trauma surgery in seven patients. A proximal femur replacement was performed in 13 patients, distal femur replacement in 13, total femur in one, and knee arthrodesis in six. Clinical results and levels of silver in blood, urine and wound drains were examined.

Results: Minimum follow-up of the patients was one year (average 25.9 months).

There was no infection during the first two years after surgery in the 12 patients who received a silver-coated megaprosthesis and had no previous history of infection. An infection developed in one patient at 25 months after surgery following two further surgical procedures.

Infection recurred at seven months and 24 months in two out of the 21 patients (9.5%) who had received the implant because of previous septic complications.

There was no clinical evidence of argyria, and no local or systemic side effects related to silver were detected.

Mean levels of silver ranging from 0.41 to 5.33 μg/L in blood and from 0.28 to 0.86 μg/L in urine were detected at 24 h to 36 months after surgery.

Conclusions: Silver-coated megaprostheses showed promising results in this series in terms of prevention of infection in a high-risk group of patients, many of whom had a history of infection. No side-effects were detected. The circulating silver levels confirm both the persistence of silver-coating activity after three years and the safety of silver-coated implants. Longer follow-up and larger series are needed.

Introduction

Infection in megaprostheses remains an unsolved problem, with a rate of occurrence ranging from 5% to 12% [1–8].

In the last few decades, many attempts have been made to reduce the incidence of infection in orthopaedic joint replacement surgery. Methods used include systemic antibiotic prophylaxis, local delivery of antibiotics using antibiotic-loaded cement and, more recently, a resorbable antibiotic-loaded hydrogel to be applied on the surface of non-cemented prostheses [9,10]. The surgical environment has been improved with the introduction of laminar flow technology, and a better separation between the surgical field and operating room personnel has been achieved with the availability of surgical body exhaust suits, although data about the effectiveness of these innovations are varied [11,12].

Nonetheless, the rate of infection remains high in megaprosthesis surgery. Recent research in this area has focussed on the possibility of producing implants that are able to defend themselves against pathogens through the introduction of bioactive coatings with antibacterial properties. Different substances are being tested for this purpose, including antibiotics like

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vancomycin, gentamicin, tobramycin and linezolid, and other substances like nitric oxide, iodine and silver, the anti-infective use of which dates back millennia in human history [13–20].

Silver, with its well-known antimicrobial properties and a low toxicity profile, seems to be particularly promising. Silver-coating has been applied recently on several medical devices, including vascular prostheses, vascular catheters, cardiac valve sewing rings, surgical sutures, urinary catheters, endotracheal tubes and wound dressings [21]. Also, orthopaedic silver-coated megaprostheses have passed the experimental phase and reached clinical application, but just a few series have been reported so far [22–26].

We decided to review our series of silver-coated megaprostheses, dating from 2010, to try to answer the following questions: Are silver-coated megaprostheses effective in reducing the incidence of postoperative infections? For how long is silver released from the prosthesis surface? What are the levels of silver ions in blood and urine in the postoperative period and during follow-up? Are there adverse effects of the use of silver-coating on orthopaedic megaprostheses?

Materials and methods

In 2010 the authors began to use a silver-coated megaprosthesis in selected cases of lower limb resections. The prosthesis was developed, as a custom-made device, by Waldemar Link and was based on the Mega C prostheses system, with the addition at the titanium non-articulating surfaces of an innovative silver coating composed of two layers: a deep basic layer of silver (1 μm thick) and a hard top layer of TiAg20 N (0.1 μm thick). The coating is called PorAg® (Porous Argentum). This particular double layer creates an oligodynamic protective cover directly at the prosthesis surface through a controlled electrochemical reaction that produces silver ions and electrons that stay near the surface. In contrast, a pure silver coating produces a non-controlled random release of metal ions and cell-toxic nano–silver in the interstitial environment around the prosthesis.

A total of 48 patients received a Porag megaprosthesis from June 2010 to August 2015.

To evaluate the use of this megaprosthesis and its efficacy in preventing postoperative infection, any patients with a follow-up of less than one year were excluded from the evaluation, unless an infection had occurred within the first 12 months. One year is an inadequate follow-up to evaluate overall incidence of infection in a series of prostheses, but it can be considered adequate to evaluate early postoperative infection, particularly infections in which seeding was likely to occur during surgery [27]. Thus, included in the evaluation were only the patients who received surgery from 2010 to August 2014, which was a total of 34 patients. One patient was lost to follow-up a few months after surgery and was excluded from the study, so 33 patients were included in the final evaluation.

A silver-coated prosthesis was chosen for the following causes:

- septic failure of previous megaprosthesis: eight patients
- septic complication after fracture: seven patients
- septic failure of previous standard joint arthroplasty: six patients
- oncological resection with patient at particular risk of infection complication: eight patients
- non-oncological resection with patient at particular risk of infection complication: four patients.

Patients were considered at particularly high risk of infection if they had one or more of the following: immunodepression, previous local radiotherapy, lymphoedema, widespread oncological disease, vascular disease or multiple previous surgical procedures.

A total of 15 of the 33 patients were affected by an oncological disease (five patients had osteosarcoma, two patients had chondrosarcoma, one patient each had pleomorphic sarcoma of bone, hemangioendothelioma of bone, lymphoma and metastasis from lung carcinoma; four patients had soft tissue sarcoma involving bone or associated to pathological fracture of irradiated bone). Eight of these patients received a silver-coated implant at the time of tumour resection; in the remaining seven patients a silver-coated prosthesis was implanted following a septic complication after the initial implant of a conventional megaprosthesis.

A total of 18 patients were affected by non-oncological diseases (following arthroplasty or trauma surgery). Fourteen of them received a silver-coated implant because of septic complications following previous surgeries; the remaining four patients had no history of previous infection.

Among the 21 patients (irrespective of their oncological status) who had suffered a previous infection, the septic complication followed one or more arthroplasty surgeries in 14 patients and surgery for trauma in seven patients. Before implanting a silver-coated megaprosthesis, infection was treated using a two-stage procedure in 14 patients (11 who had previous arthroplasty surgery and three who had previous trauma surgery) and using a one-stage procedure in seven patients (three who had previous arthroplasty surgery and four who had previous trauma surgery).

A proximal femur megaprosthesis was implanted in 13 patients, a total femur megaprosthesis in one patient, a distal femur megaprosthesis in 13 patients, and a knee arthrodesis megaprosthesis in six patients.

Perioperative antibiotic prophylaxis was performed with vancomycin 1 g and tobramycin 100 mg at induction of anaesthesia and twice-a-day thereafter for 5 days, followed by oral antibiotics (amoxicillin 875 mg and clavulanic acid 125 mg) twice-a-day for two to three weeks.

The mean age of the patients was 55 years (range 17–82 years); 22 patients were male, 11 female.

Patients were evaluated clinically and radiologically at follow-up. In cases of clinical or radiographical suspicion for infection, further studies were added, including serological examinations and further specific imaging techniques, eventually leading to microbiological cultures.

Diagnosis of periprosthetic infection was performed according to the criteria proposed by the International Consensus Group on Periprosthetic Infections [28]. The Consensus Group defined two major criteria (two positive periprosthetic cultures with phenotypically-identical organisms; a sinus tract communicating with the joint) and five minor criteria (elevated serum C-reactive protein and erythrocyte sedimentation rate; elevated synovial fluid white blood cell count or change on leukocyte esterase test strip; elevated synovial fluid polymorphonuclear neutrophil percentage; positive histological analysis of periprosthetic tissue; a single positive culture). An infection was diagnosed when one of the major criteria was met or three out of the five minor criteria were met.

In a subset of patients (see Results Section) the concentration of silver ions in body fluids was evaluated as follows:

- preoperative (blood, urine)
- 24 h postoperative (blood, urine, drainage)
- 10 to 14 days after surgery (blood, urine)
- 3 months, 6 months, 12 months, 24 months, 36 months, 48 months after surgery (blood, urine).

The analysis was performed using inductively coupled plasma mass spectrometry at the Laboratory of Experimental and Clinical Toxicology, Toxicology Unit, Pavia Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri

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Table 1
Silver in blood and urine.

BLOOD µg/L	Preop	Postop 24 h	14 days	3 mths	6 mths	12 mths	24 mths	36 mths
mean	0,14	0,41	3,59	4,8	2,99	2,98	5,33	2,09
min	0	0,02	0,4	0,2	0,44	0,24	0,82	0,3
max	0,26	2,74	12	20	10	9	20	3,7
St. dev	0,07	0,58	3,18	5,42	2,71	2,85	6,3	1,34
n. pts	18	21	15	17	13	14	8	5
URINE µg/L	Preop	Postop 24 h	14 days	3 mths	6 mths	12 mths	24 mths	36 mths
mean	0,09	0,28	0,55	0,49	0,32	0,86	0,79	0,47
min	0	0	0,02	0,04	0,05	0,05	0,10	0,1
max	0,33	1,10	1,35	1,40	1,3	7,5	5,0	1,19
St. dev	0,11	0,29	0,42	0,43	0,40	1,89	1,7	0,47
n. pts	19	20	14	17	15	15	8	5

Levels of silver in blood and urine (µg/L) in patients bearing a silver-coated megaprosthesis from preoperative day to three years after surgery. Mean, minimum and maximum detected values are reported, together with the number of patients examined.

Foundation, Pavia, Italy, according to a method already validated for samples of human tissues and fluids [29].

The study was performed in accordance with the 1975 Declaration of Helsinki. All the patients gave informed consent. The study was retrospective and no objection/exception was formulated by the local institutional ethics committee.

Results

Follow-up ranged from 12 to 56 months (average 25.9 months). One patient who had metastasis from lung carcinoma and received a proximal femur megaprosthesis died of disease 16 months after surgery.

There was no infection during the first two years after surgery in the 12 patients who received a silver-coated megaprosthesis and had no previous history of infection. An infection developed in one patient at 25 months after surgery following two further surgical procedures (two revisions for hip instability in a patient with a proximal femur reconstruction). The causative germ was *Staphylococcus epidermidis*. A one-stage revision was performed and the patient is apparently free of infection but at just a few months from surgery at the time of the present paper. There were no infections reported in patients who did not undergo further surgeries.

Two of the 21 patients (9.5%) who received the Porag implant (proximal femur in one patient, total femur in the other patient) because of previous septic complications had recurrent infection at seven and 24 months, respectively, after the date of implant. In one of the two patients, infection followed further surgical procedures (an acetabular revision for traumatic loosening of the cup in the patient bearing a total femur); the isolated germ (*Enterococcus faecium*) differed from previous infection (*Staphylococcus aureus*). In this patient a further one-stage revision was performed using a new Porag implant; this ultimate revision was too recent to evaluate results at the time of the present paper (one month). In the second patient, who had a history of multiple surgeries, a conservative approach using medical treatment was chosen and is ongoing. The isolated germ in this patient was *Staphylococcus aureus*.

Aseptic femoral stem loosening occurred in one patient who had undergone distal femur reconstruction. The prosthesis was revised at 24 months after surgery.

Among the 15 patients affected by oncological disease, tumour recurrence occurred in one patient who had distal femur osteosarcoma, leading to amputation 25 months after surgery.

One patient who had undergone distal femur reconstruction presented in the first months after surgery a persistent drainage from a site of the surgical scar with serous secretion and negative cultures from multiple subsequent swabs. This resolved with medical treatment and the patient is being monitored.

In another patient who underwent knee arthrodesis reconstruction. a localised tumefaction with dehiscence of the wound occurred at three years after surgery; the lesion healed after surgical debridement (with negative microbiological cultures from debridement specimens) and the patient did not show clinical or serological signs of infection at nine months after the debridement procedure.

There were no clinical signs of argyria or peripheral neuropathies in any of the patients in the study. No other side effects of silver could be detected in any patient.

The levels of silver in body fluids are shown in Table 1. This table also shows the numbers of samples examined at each follow-up time. A graphical description of data is shown in Figs. 1 and 2.

Preoperative levels of silver ranged from 0 to 0.26 µg/L in blood and from 0 to 0.33 µg/L in urine. An increase in average silver levels could be detected within the first few hours after surgery, but this increase became more evident at 14 days and at 3 months after surgery, with a higher raise in blood than in urine. These values showed only a slight progressive reduction in the subsequent evaluations at 6 and 12 months. In the eight patients examined at 24 months a different pattern was seen with half the patients showing a decrease and half the patients showing an increase in silver levels compared with the values at one year.

Mean levels of silver after surgery ranged from 0.41 to 5.33 µg/L in blood and from 0.28 to 0.86 µg/L in urine. The highest value found in blood was 20 µg/L in two different patients at 3 and 24 months after surgery, respectively; the highest value in urine was 7.5 µg/L in one patient at 12 months.

A mean silver concentration of 2.09 µg/L in blood and 0.47 µg/L in urine was still detectable in the five patients examined at three years after surgery.

Levels of silver were also detected in fluids from wound drains in 17 patients; values ranged from 0.48 to 78.0 µg/L, with an average of 27.8 µg/L.

There was a high interpatient variability at all follow-up examinations (see Table 1). There was no correlation between levels of silver in the blood and prosthesis length at 14 days and three months after surgery, whereas a moderate correlation was present at one year ($r = 0.616$; $P < 0.05$; Pearson Correlation Test).

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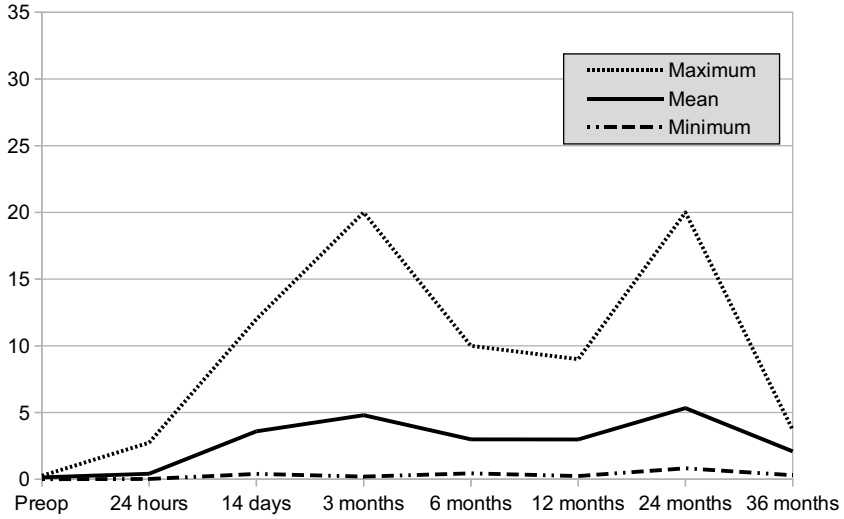

Fig. 1. Silver levels in blood (μg/L) in patients bearing a silver-coated megaprosthesis; mean, lowest and highest detected values are reported.

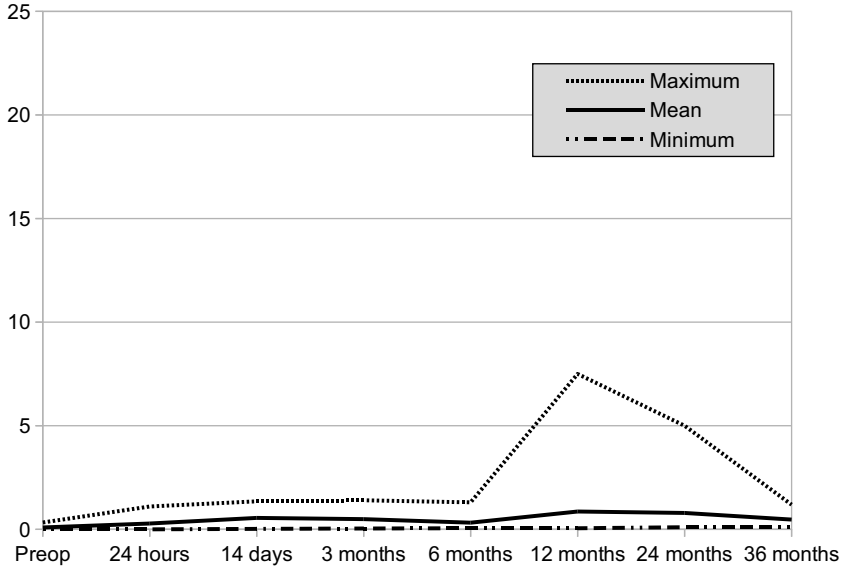

Fig. 2. Silver levels in urine (μg/L) in patients bearing a silver-coated megaprosthesis. Mean, lowest and highest detected values are reported.

Discussion

There is strong biochemical and experimental evidence for an antibacterial action of silver and this metal has been shown to act against bacteria in several ways [21,30]. Silver ions bind strongly with bacterial wall proteins, perhaps because of their interaction with thiol groups, causing damage to the bacterial wall [31–34]. Furthermore, silver can complex with DNA and cause precipitation of DNA within bacteria; it can also lead to the formation of reactive oxygen species that are toxic to bacterial cells [31,35,36]. In addition, silver coating on titanium surfaces has been demonstrated to inhibit *in vitro* biofilm formation by *Staphylococci* [37]. As silver is associated with multiple mechanisms of antibacterial action, the development of bacterial resistance to silver may be less likely compared with resistance to antibiotics as these usually act with a single mechanism [38].

Few clinical series of silver-coated orthopaedic megaprostheses have been reported so far; however, all the reported data indicate that this coating lowers the incidence of postoperative infection [22–26]. Hardes et al. reported a lower incidence of infection with silver-coated prostheses (5.9%) as primary implants compared with traditional titanium megaprostheses (17.6%) [23]. In a smaller series, Hussman et al. confirmed the effect of silver in reducing postoperative infections [24].

Wafa et al. analysed megaprostheses implanted as primary surgical procedures and those implanted after infection and reported a lower incidence of infection with the use of silver-coated megaprosthesis (11.8%) compared with controls (22.4%) [26]. In this series, Wafa found the rate of infection in primary surgeries was similar in the two groups, but a statistically significant difference was found for megaprostheses implanted after infection, either in one-stage procedures (5.1% in silver-coated prostheses versus 12.5% in conventional megaprostheses)

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or two-stage procedures (15.0% in silver-coated prostheses versus 42.9% in conventional megaprostheses) [26].

In the current series, only 12 megaprostheses were implanted in patients who had no previous septic complications, but were at high risk for infection because of systemic or local conditions. No postoperative infections occurred in the first two years after surgery in primary implants, and only one infection occurred at 25 months after two further surgeries. In comparison, our previous analysis of 200 megaprostheses implants after tumour resections showed a 5% incidence of infection during the first year after surgery [8]. The findings in the current study are promising for the use of silver-coating, but the number of patients is small and further follow-up and larger patient numbers are needed to infer conclusions.

Most of the implants in our series (21 out of 33) were applied in patients who had suffered previous septic complications. Infection recurred in two of the 21 patients, which is a 9.5% rate of re-infection, at a minimum follow-up of more than one year (average 27.6 months). This is a promising result as this type of surgery is associated with very high risk for septic failure, like megaprosthetic reconstructions after previous infection [39,40]. Our result matches that reported by Wafa et al., who found a cumulative 8.47% rate of infection recurrence in one-stage or two-stage revisions with silver-coated megaprostheses compared with 22.9% in revisions with non-silver-coated implants [26].

Our paper has several limitations: the number of patients is low and higher numbers are needed to confirm clinical and laboratory results; the follow-up is too short to evaluate long-term results; and the heterogeneity of the causes leading to the implant of a silver-coated megaprosthesis precludes thorough analysis of the results. Nonetheless, our data are in agreement with previous reports of a positive effect of silver-coating in reducing the incidence of postoperative infection [23,26].

Few data are reported in the literature about the levels and persistence of silver ions in body fluids of patients. Hussman et al. examined silver levels in wound fluid from redon drains and in blood and reported mean blood levels of 30 μg/L and 20 μg/L at 7 and 14 days after surgery, respectively (no other timepoints were used) [24].

Glehr et al. found in the blood of 20 patients an average level of silver of 15.9 μg/L (range 6.5–40 μg/L), but the time of the blood examination during follow-up was not elucidated in the paper [25]. Hardes et al. in a series of 20 megaprostheses reported a mean silver concentration in blood of 2.8 μg/L (range 0.8-9.12 μg/L) at two weeks after surgery, with subsequent mean silver levels ranging from 1.93 to 12.98 μg/L from the third to the 24th month [22]. The highest single value was 56.4 μg/L in a patient at 15 months after surgery.

Levels reported by Hardes are lower than those reported by Hussman and Glehr, even though these three authors used the same prosthesis (Mutars, Implantcast) [22,24,25].

The current study findings using a different prosthesis (Porag MegaC, Waldemar Link) show mean levels of circulating silver in blood from two weeks after surgery to 36 months range from 2.09 to 5.33 μg/L. Although there was high variability in silver levels in the current study, the mean silver concentration in the blood of patients bearing a Porag MegaC prostheses seemed to be lower than previously reported for Mutars prostheses and had lower peaks (the highest level detected in a patient was 20 μg/L compared with 56.4 μg/L). This may be because of the particular surface characteristics of Porag MegaC prosthesis and could be an advantage to lower the incidence of argyria, which was not detected in the series of Hardes, but reached 23% in the series of Glehr with Mutars prostheses [23,25].

Silver coating of Mutars prostheses is achieved by galvanic deposition of elementary silver [23]. In contrast, the surface of Porag MegaC prostheses is modified to create a double layer of silver and TiAg20 N to enable a controlled electrochemical reaction that produces silver ions and electrons near the surface. This may explain a more stable and limited release of silver in circulating body fluids, with mean blood silver levels in our series remaining between 2.09 and 5.33 μg/L from 2 weeks to 3 years after surgery, whereas mean circulating silver levels reported for Mutars prostheses were higher, with a wider fluctuation and higher peak values for a single patient [22,24,25]. Further clinical data and experimental confirmation of this are needed to support this hypothesis.

Fluids from wound drains showed 10-times higher silver concentrations compared with circulating blood and even higher levels are likely to occur at the prosthesis surface: this should create the conditions for the occurrence around the prosthesis of silver concentrations able to inhibit the growth of bacteria, even if data about the actual silver concentration at the prosthesis–host interface are not available.

The Agluna silver-coating process used for Stanmore implants also involves an engineered surface modification, but no data on silver concentration in body fluids with these implants have so far been published to our knowledge [26].

Data from the current series and from Hardes' series show that clinically significant levels of silver are still present in blood and urine as long as two years (Hardes' series) and three years (the current series) after surgery; therefore, a long-lasting local active effect against bacteria colonisation can be supposed [22].

This long-lasting antibacterial effect is likely to occur without causing significant local and systemic adverse effects. No clinical adverse effects could be detected in the patients in the current study, as was the case in earlier studies in which this issue was addressed, with the exception of argyria [22,24,25].

Health risks associated with systemic absorption of silver seem to be low and the threshold of toxicity of silver in body fluids, as far as it is actually known, is higher than levels found in circulating or drainage fluids in the current series and in previously reported series [30,41].

A possible local adverse effect of silver usage is argyria, in which the skin becomes blue or bluish-grey. It is usually a local effect, but can also be diffuse.

Data about argyria in patients bearing silver-coated megaprostheses are inhomogeneous, with a reported incidence ranging from 0% to as high as 23% [22,24,25].

A direct correlation between silver levels in blood and argyria could not be demonstrated and development of argyria could be, at least partially, idiosyncratic [25].

There were no signs of argyria in the patients in the current study.

Peripheral neuropathies have also been reported as side-effects of silver, but no clinical signs of neurological complications occurred in the current patient series or in the other series of silver-coated megaprostheses [22,24,25,42,43]. Further investigations with electromyographic studies are required to rule out the possibility of the presence of subclinical neuropathies.

An effect of silver on renal or hepatic function is also possible, but it has not been observed so far in silver-coated megaprostheses [22,24,25,41,44].

The variability in circulating silver levels between patients was not apparently determined, or at least was only partially determined, by the different amounts of silver implanted due to differences in prosthesis length, because there was no significant correlation between levels of silver and length of prosthesis at 14 days and 3 months after surgery, and only a moderate correlation was detectable at one year. Hardes and Glehr also found no evident correlation between the amount of silver on the prosthesis and silver levels in blood [22,25]. Hussman reported a statistically significant correlation at 14 days after surgery, but not at 7 days [24].

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Conclusions

The results of the current series of silver-coated megaprostheses, as with earlier similar series, should be considered as preliminary because of the short follow-up and the limited number of patients. Nonetheless, silver-coating of megaprostheses seems to be associated with a lower incidence of infection in a surgery that has very high risk of septic complications, which can have devastating effects on patient quality of life and cause high additional economic burdens on the National Health Services.

There were no local or systemic side effects of silver in the current series of patients, which confirms the low toxicity potential of silver in clinical use.

Silver is obviously not the 'final solution' for the problem of septic failures in megaprostheses surgery, but it can be a useful additional weapon for patients who are at particularly high risk because of previous septic complications or local or systemic conditions.

If the effectiveness of silver-coating is confirmed in future studies, all patients undergoing resection and megaprosthetic reconstruction may become candidates for a silver-coated implant in the future. Further and larger studies are needed.

Conflict of interest

One of the Authors (Rodolfo Capanna) has a patent registration about a Waldemar Link product but not about Porag coating, which is the specific issue of this study. None of the remaining Authors has any potential conflict of interest.

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